1039 Neurohormones, Cardiac Function, and Pericardial Delivery

Monday, March 30, 1998, Noon–2:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: Noon–1:00 p.m.

MONDAY POSTER

1039-23 Melatonin, a Pineal Hormone With Antioxidant Property, Protects Against Adriamycin Cardiomyopathy in Rats

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Background: The clinical use of adriamycin (ADR) is limited by its cardiotoxicity in which free radicals and lipid peroxidation may be involved. Melatonin (MEL) has gained increasing interest as a strong antioxidant. Accordingly, the protective effects of MEL against ADR cardiomyopathy was evaluated.

Method: Male Sprague-Dawley rats were divided into 4 groups as follows: ADR (ADR treated, cumulative dose 15 mg/kg bw, ip, for 2 weeks), MEL (MEL treated, cumulative dose 84 mg/kg bw, ip), MEL + ADR (MEL + ADR treated), and CONT (control). After 3 weeks of post treatment observation, their cardiac performance was assessed, and their hearts were used to study myocardial lipid peroxidation by measuring thiobarbituric acid reactive substance (TBARS) along with ultrastructure.

Results: MEL reversed the ADR induced changes in myocardial ultrastructure as well as parameters shown below.

	CONT	ADR	MEL	MEL + ADR
HW/BW ratio	2.63 ± 0.05	2.39 ± 0.05*	2.61 ± 0.06	2.71 ± 0.05
Ascites (ml)	0	31.7 ± 6.3**	0	3.2 ± 2.2
SBP (mmHg)	124.4 ± 2.6	107.4 ± 4.1*	126.3 ± 3.9	124.1 ± 3.2
FS (%)	56.8 ± 1.1	36.4 ± 2.3**	53.4 ± 1.6	50.6 ± 1.1
Mortality (%)	0	23*	0	0
TBARS (nmol/g heart)	51.3 ± 1.1	83.8 ± 2.2**	45.9 ± 1.6	51.4 ± 2.0

Data are mean ± SEM. **p < 0.01, *p < 0.05 vs all other groups. HW/BW: Heart weight/body weight. SBP: Systolic blood pressure. FS: Fractional shortening

Conclusion: MEL may be highly effective in protecting against ADR cardiomyopathy by preventing lipid peroxidation.

1039-24 Tumor Necrosis Factor-α Induces Contractile Dysfunction in Conjunction With Nitric Oxide Production in Conscious Dogs

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Tumor necrosis factor (TNF)-α promotes elaboration of the inducible isoform of NO synthase (iNOS); however, the relationship between subsequent NO production and the development of contractile dysfunction in vivo is not known. Accordingly, six chronically instrumented, conscious dogs pretreated with propranolol (2 mg/kg) and atropine (2 mg) were studied before and after 1 hour infusion of TNF-α (40 μg/kg). LV contractility was determined by end-systolic elastance, E_{es} (mm Hg/ml), and plasma nitrite + nitrate levels (NO_2 +NO_3; μM) by vanadium reduction. Dogs were killed 24 hour after TNF-α or saline; hearts were frozen and assessed for iNOS protein levels (Western blotting), iNOS enzyme activity (conversion of ^{3}H-arginine to ^{3}H-citrulline in the presence of EGTA+EDTA), localization of iNOS (immunohistochemistry, IHC), and NF-κB, a transcription factor involved in the upregulation of iNOS (electrophoretic mobility shift assay). In TNF-α treated dogs, we observed a 4-fold increase in NF-κB levels, a 3-fold increase in myocardial iNOS protein, and an 18-fold increase in enzymatic activity ($P < 0.001$ for each). IHC localized iNOS predominantly to vascular endothelium and smooth muscle and less intensely to cardiomyocytes.

	Pre-TNF-α	1 h post	7 h post	24 h post
E_{es}	5.4 ± 0.4	7.9 ± 1.4*	5.2 ± 0.5	3.2 ± 0.4*
NO_2 +NO_3	17.6 ± 2.5	14.7 ± 1.4	18.6 ± 1.8	38.5 ± 6.4*

*P < 0.05 Vs corresponding pre-TNF-α

We Conclude: TNF-α administration upregulates functionally active iNOS in the heart, possibly through activation of NF-κB. Increased plasma metabolites of NO strongly correlate with in vivo cardiac depression after TNF-α.

1039-25 Positive Inotropic Effect of Bradykinin: Role of Cardiac Endothelium, Nitric Oxide, Prostaglandins and Endothelin

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Background: Bradykinin (Brad) causes endothelium-dependent vascular smooth muscle relaxation and may explain some of the beneficial cardiac effects of angiotensin converting enzyme inhibitor therapy. Brad receptors are also present on cardiomyocytes. However, the inotropic effect of Brad on myocardium, in particular role of endocardial endothelium (EE), mediators released by EE-nitric oxide (NO), prostaglandins (PG) and endothelin, and interaction with concomitant β-adrenergic stimulation have not been investigated.

Methods: We examined myocardial effects of Brad (10^{-9} M to 10^{-5} M) in isolated cat papillary muscles (Krebs-Ringer 1.25 mM Ca^{++}, 35°C, enalaprilat: 5×10^{-5} M, atenolol: 2×10^{-5} M) before (+EE: n = 7) and after selective damage of EE (−EE: n = 7; 1s immersion in Triton-X, 0.5%). To investigate role of NO, PG and endothelin, Brad was also added in subgroups of +EE muscles incubated with L-NA (3×10^{-6} M, n = 8), indomethacin (INDO: 10^{-6} M, n = 8) or BQ123 (10^{-6} M, n = 7) respectively.

Results: (mean ± SE, Δ% baseline) In +EE, Brad induced an dose-dependent increase in peak active tension (AT: 10^{-5} M = 9.3 ± 3.1) with no change in time to half relaxation (0.7 ± 1.4). This response was blocked by the bradykinin receptor antagonist (HOE 140: 10^{-7} M, n = 3) and was absent in -EE. The inotropic response to Brad was not inhibited by LNA, INDO or BQ123 alone but was inhibited by LNA + INDO (Brad: 10^{-5} M; AT = 1.0 ± 1.6). Isoproterenol (3×10^{-7} M)-induced increase in AT (14.4 ± 2.0) was abolished by Brad (10^{-5} M) (0.2 ± 4.2), which was not modified by LNA + INDO (0.3 ± 4.3).

Conclusion: Brad induced a cardiac endothelium-dependent positive inotropic myocardial effect with no effect on relaxation, which was mediated by both NO and PG. Brad abolished the effect of concomitant β-adrenergic stimulation, independent of NO and PG.

1039-26 Atrial Natriuretic Peptide Decreases Contractility and Intracellular pH in Adult Ventricular Myocytes

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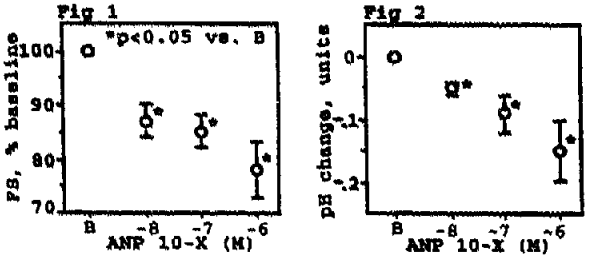
Atrial natriuretic peptide (ANP)-cGMP signaling modifies cardiac function by natriuresis and vasodilation but inotropic effects are controversial. We studied effects of ANP on cell shortening and intracellular signaling in HEPES-buffered adult ventricular rat myocytes (n = 26) paced at 0.5 Hz. At baseline (B), fractional cell shortening (FS) was 7.0 ± 0.2% and intracellular pH (pHi, SNARF-1) was 6.92 ± 0.05. ANP caused a dose-dependent depression of contractility (Fig. 1), associated with intracellular acidification (Fig. 2). In cells loaded with Fluo-3 (n = 5), ANP caused no change in systolic $[Ca^{2+}]_i$.



Summary: ANP directly depresses contractility via intracellular acidification and decreases myofilament $[Ca^{2+}]$ sensitivity. Similar to negative inotropic action of nitric oxide, this may be related to cGMP-mediated disabling of forward Na^+-H^+ exchange.

1039-27 Pharmacokinetics of Agent Distribution From the Pericardial Space: Effects of Agent Size and Validation of a Mathematical Model for Epicardial Penetration

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Recent data have demonstrated reduction of restenosis in the porcine model by intrapericardial delivery of diazeniumdiolated albumin (NONO-Alb). The bioactivity of intrapericardial agents will be importantly modulated by their residence time as well as penetration into epicardial tissue. We thus evaluated the dependence of residence half-life (RHL) on molecular weight (MW)

of agents, and developed and tested a reaction-diffusion model for myocardial penetration from the pericardial space. ^{131}I-Lysyl-lysine (LL), MW 420 D; ^{131}I-NONO-Alb, MW 73 kD; and ^{99m}Tc-macroaggregated albumin (MAA), 30 μm diameter were delivered into the porcine pericardial space (n = 10) by a transmyocardial route using a helix-needle catheter. Washout was assessed over 72 h by serial scintigraphy to define agent loss from the region of interest. Epicardial-endocardial concentration gradients (n = 5) established 2 h after agent delivery were assessed by measuring count rates of myocardial tissue series obtained by cryosectioning tangential to the epicardial surface. A mathematical model was developed based on a reaction-diffusion equation describing agent transfer into myocardium as a function of interstitial diffusion, transcapillary washout, penetration depth, and time. RHL was 98 ± 26 h for MAA, 22 ± 4 h for NONO-Alb, and 4.6 ± 0.5 h for LL. Sharp transmural concentration gradients were found for LL, with a penetration half-depth of 2.5 ± 0.1 mm; these profiles were closely fit by our mathematical model (r ≈ 0.95). In conclusion, physical size of agents strongly influences intrapericardial residence time; and transmural concentration gradients are steep, and well-modeled in terms of diffusion and washout. These pharmacokinetic and tissue penetration characteristics will help to define appropriate agents and suitable targets for intrapericardial therapy.

1040 Amyloid and Inflammatory Myocardiopathy

Monday, March 30, 1998, Noon–2:00 p.m.
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1040-41 Long-term Survival in Patients With Primary Systemic Amyloidosis With Biopsy-proven Cardiac Involvement

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Background: Prognosis in primary systemic amyloidosis with cardiac involvement is poor with a reported median survival of 5 months. The purpose of this study was to determine the frequency of long-term survival (≥5 yrs) in patients (pts) with primary systemic amyloidosis with biopsy proven cardiac involvement.

Methods: A review of all patients with primary systemic amyloidosis with biopsy proven cardiac involvement was performed.

Results: One-hundred and fifty-four pts with primary systemic amyloidosis with a positive cardiac (153 endomyocardial, 1 pericardial) biopsy for amyloid infiltration were seen from 1965 to 1997. Ten pts (6%) were found to have long-term survival, with a median of 138 months (range 76–181). Seven pts survived ≥10 yrs and 6 of the 10 pts were alive at last follow up. All pts with long-term survival received chemotherapy. Median survival of the remaining 144 pts was 6 months. Initial EF was significantly higher (55 ± 12 vs 47 ± 14%, p = < 0.001) and mean mitral deceleration time was longer (196 ± 71 vs 166 ± 45 msec, p = < 0.001) in pts with ≥5 yr survival. Initial septal thickness was not significantly different in those with > or < 5 yr survival (15 ± 4 vs 16 ± 3 mm).

Conclusion: Despite overall poor prognosis, long-term survival is possible in treated pts with primary systemic amyloidosis and cardiac involvement including survival of ≥10 years in 4% of pts. Higher initial EF and longer mitral deceleration time were present in pts with long-term survival.

1040-42 A Comparative Echocardiographic Study of Primary, Familial and Secondary Amyloidosis

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Background: Amyloidosis (A) is characterized by the deposition of specific proteins in various organs. Currently recognized types include primary, secondary and familial each of which may involve the heart.

Material and Methods: Left ventricular (LV) morphology, LV diastolic and systolic function and right ventricular (RV) size and systolic function were echocardiographically (M-mode, 2D, pulsed and continuous Doppler) assessed in 28 patients with primary, 17 with familial and 11 with secondary A. To study disease progress in primary A, all patients underwent a repeat examination after a period of 15 ± 6 months.

Results: Interventricular septal thickness (mm) was greater in primary or familial than in secondary A (14.1 ± 2.3 vs 13.9 ± 1.98 vs 12.27 ± 1 respectively, p < 0.002) while LV posterior wall thickness (mm) was similar in the three groups (13.7 ± 2.4 vs 13.3 ± 1.7 vs 12.18 ± 1.1, p = NS). LV fractional shortening (FS, %) was reduced in primary compared to familial (29.8 ± 10.2 vs 36.2 ± 6.5 vs p < 0.05. The transmitral flow velocity (TFV) pattern was compatible with abnormal relaxation in most patients of the 3 groups [primary: 16 (57%), familial: 11 (64.7%), secondary: 8 (72%), p = NS]. RV thickening was present in 13 (46.4%) patients with primary, 6 (35%) with familial and 1 (9%) with secondary A. RV dysfunction was present in 8 (28.6%), 2 (11.8%) and 0 patients respectively. Repeat examination of patients with primary A revealed deterioration of LV systolic function (FS = 23.6 ± 8.8, p < 0.05 vs baseline) and increased frequency of LV restriction in TFV profile (53.6% vs 25% at baseline, p < 0.05).

Conclusions: Primary amyloidosis causes more severe cardiac involvement than the familial or secondary types. Progression of primary amyloidosis is rapid and characterized by deterioration of both left ventricular diastolic and systolic function.

1040-43 Echocardiographic Identification of Cardiac Amyloidosis Patients Capable of Undergoing Intensive Treatment With Intravenous Melphalan Therapy

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Background: Primary amyloidosis (AL) is a protein deposition disease which carries a poor prognosis, especially in patients (pts) with cardiac involvement. Intravenous melphalan (IVM) followed by autologous stem cell transplantation is an aggressive therapy which may produce disease remission and improve survival.

Methods and Results: To determine if pts with cardiac AL can be safely treated with this therapy, we studied the echocardiograms of 64 consecutive pts undergoing IVM and measured septal and posterior wall (PW) thickness, LV end-diastolic diameter (LVEDD), LV mass, and fractional shortening (FS). Cardiac AL, defined as wall thickness >1.1 cm, was present in 30 patients. After 6 months of follow-up, 15 pts (50%) with cardiac amyloid had died compared to 5 pts (15%) without cardiac disease (p = 0.006). Of the 30 pts with cardiac AL, 9 died in the peri-therapy period (≤1 month) and 15 of the remaining 21 pts were alive at 6 months.

	Survival ≤ month (n = 9)	Survival > 1 month (n = 21)	p value
Septum (cm)	1.43 ± 0.22	1.30 ± 0.13	0.07
PW (cm)	1.38 ± 0.16	1.26 ± 0.08	0.01
FS (%)	24.7 ± 8.5	33.6 ± 11.3	0.04

There was no significant difference between the two groups with respect to LVEDD or LV mass.

Conclusion: Pts with cardiac amyloid should not all be excluded from intensive IVM since careful echocardiographic evaluation prior to therapy can identify pts at high risk for peri-treatment mortality.

1040-44 Incidence of Dilated Cardiomyopathy and Detection of HIV in the Myocardial Cells in a Large Population of HIV-positive Subjects: A Long-term Clinical and Echocardiographic Follow-up

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Background: Human Immunodeficiency Virus (HIV) disease is increasingly recognized as an important etiologic factor in Dilated Cardiomyopathy (DC). Aim of the study was to assess the incidence of echocardiographically-diagnosed DC over time in a large and selected population of HIV-positive subjects, correlating the morphologic and functional parameters with clinical and virologic data.

Methods: Nine hundred and fifty two asymptomatic HIV-positive subject were long-term followed-up by clinical and echocardiographic examinations, which were performed, respectively, every three and six months. DC was defined as the presence of diffuse left ventricular hypokinesia (ejection fraction <45%) and left ventricular dilatation (left ventricular end-diastolic volume index >80 ml/m^2). The patients with echocardiographic diagnosis of DC underwent endomyocardial biopsy (EMB) for histologic, immunohistologic and virologic examination.

Results: During the follow-up period (60 ± 5.3 months), echocardiographic diagnosis of DC was made in 76 patients (7.9%), with a mean incidence of 1.2 new cases/month and 15.3 new cases/year. The relative risk for development of DC was greater in homosexuals patients, in those with a CD4+ cell count <400/mm^3 and in those who received therapy with zidovudine. All patients with echocardiographic diagnosis of DC underwent EMB. Histological

MONDAY POSTER